

REMARKS/ARGUMENTS

The rejection of claims 75, 76, 78, 79, and 83 – 87 under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. (U.S. Patent No. 5,955,077) is respectfully traversed. As an initial matter, as the Examiner likely is aware, none of the new documents cited in the Notice of References annexed to the latest Office Action can be relied on as prior art documents as they were all published far after the priority date of 4th November 1998. While the Examiner has not relied on any of these documents as such, it appears that the Examiner may have acquired the benefit of hindsight by reading these documents to the extent that it has been influential in maintaining a rejection relying on the Andersen et al. US Patent, but now under 35 U.S. C. § 103 (a). It is emphasized that the present inventors were the first to set out to establish whether a diagnostic test having high sensitivity and specificity for *M. tuberculosis* was feasible based on short T cell epitope-containing ESAT-6 fragments. In this regard, the Andersen et al disclosure provided no technical teaching of assistance whatsoever. **It merely confirmed that whole ESAT-6 will produce a T cell response when utilized in a skin test in guinea pigs**, and cannot be validly combined with any other reference to suggest obviousness of a peptide panel as specified by the claims in this application.

The following points demonstrate the true distance between the claimed invention and the disclosure of the Andersen et al. Patent. However, if the Examiner believes that applicants' are somehow not fully understanding the basis for the rejection, an interview by phone is requested so that applicants can gain a better understand.

1. T cell epitopes are recognized in humans in the context of HLA antigens. The Andersen et al. Patent provides no basis for even assuming that all predominant HLA specificities could be represented by at least one member of a small panel of short peptides. That this is indeed the case for a peptide panel as set forth in claim 75 is shown by data in the specification. The specification provides data showing that the panel of 8 short peptide fragments listed in claim 75 correctly identified 96% of TB patients tested (see paragraph 4 on description page 1 and Table 5 on page 29).

2. Furthermore, a major technical improvement obtained by using an ESAT-6 peptide panel compared with whole ESAT-6 is set out in Example 6. This example reports that the

peptide panel as specified in claim 75 will detect both CD4 and CD8 T cell responses while whole ESAT-6 only detects CD4 T cell responses. This is of clinical importance as well since, as also noted in Example 6, not all human TB patients generate significant CD4 T cells to ESAT-6 of infecting *M. tuberculosis*. This finding was substantiated in later work, and its implications and technical explanation are discussed in more detail in Chapman et al., AIDS, 16, pp 2285-93 (2002), specifically on page 2288 beginning at the bottom paragraph of the first column. A copy of this paper is provided. Again, it is shown that an ESAT-6 peptide panel has advantages in a clinical setting (see Table 1) by virtue of the fact that T cells from HIV positive TB patients respond well to ESAT-6 peptides, but relatively poorly to whole ESAT-6 antigen. The reasoning behind selection of the particular panel specified in claim 75 is explained at lines 14 to 117 on page 17 of the subject application.

As indicated in the appended journal paper, the advantages gained by using a peptide panel probably arise because whole ESAT-6 antigen, when added exogenously to an *in vitro* assay, is not processed and presented through the MHC Class I antigen processing pathway. This means that the processed peptides will not be presented to CD8+ T cells because such cells only recognize complexes of peptide / MHC Class I protein. On the other hand, peptides, which require minimal processing, are probably processed / presented via both Class I and II pathways.

3. The previously noted paper of Elhay et al. published in July 1988 (Elhay et al. Infect. Immun. (1988)) shows that more than 3 years after the publication of WO 95/01441 (corresponding to the Andersen et al. US Patent), Andersen et al. were not advocating use of any panel of ESAT-6 fragments for diagnostic use in humans. Rather they were suggesting at that time that a good diagnostic reagent for use with humans would be a combination of whole ESAT-6 with another protein (see again bottom of left hand column on page 3455). The Elhay paper provides data showing that a peptide from the C-terminal region of ESAT-6 is effective in a skin test in detecting T cells in guinea pigs infected with tuberculosis but this has no relevance to the peptide panel for human diagnostic set forth in the claims of the subject application. Hence, this document supports the contention that a peptide panel as now claimed was not an obvious extension of the disclosure of the Andersen et al. Patent.

In summary, it is not disputed that the Andersen et al. Patent: (a) did teach the

diagnostic utility of ESAT-6; and (b) speculated that subsequences of ESAT-6 might be similarly employed. However it is respectfully submitted that the immunological and clinical advantages achieved through the use of an ESAT-6 peptide panel as claimed, namely improved 'access' in the assay to the entire spectrum of CD4+ / CD8+ T cells, and compatibility with a broad spectrum of human HLA specificities, could not have been predicted from the Andersen teachings relied on by the Examiner. Indeed, the top of column 6 of the Andersen et al. U.S. Patent places emphasis if anything on long subsequences which might substitute for whole ESAT-6. This is very different from selecting a specific peptide panel of short peptide fragments for human diagnostic use as now claimed.

Applicants believe the claims have been demonstrated to be allowable and respectfully solicit a Notice of Allowance. In the event the Examiner does not allow the claims, an interview by telephone phone is requested so that applicants can better understand the rejection.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Robert Berliner', is written over a horizontal line.

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